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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/185,904	11/03/98	ANDERSON C	660088.420

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HM12/0425

EXAMINER	
SCHNIZER,H	
ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 04/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary

Application No.	Applicant(s)
09/185,904	Anderson et al.
Examiner	**Group Art Unit**
Holly Schnizer	1653

X Responsive to communication(s) filed on Feb 9, 2000

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) 1-101 is/are pending in the application.

Of the above, claim(s) 1-41 and 58-101 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) 42-57 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a))

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

☒ NOTICE TO COMPLY WITH SEQUENCE RULES

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Restriction/Election

1. The Election of Group II, Claims 42-57 without traverse in the Response filed February 9, 2000 is acknowledged. Therefore, Claims 1-101 are pending, Claims 1-41 and 58-101 are withdrawn from consideration as being directed to a non-elected invention, and Claims 42-57 will be examined on the merits.

Notice to Comply with Sequence Rules

2. The disclosure is objected to because of the following informalities: The application does not fully comply with the sequence rules (37 C.F.R 1.821-1.825). The errors detected when processing the CRF diskette are indicated in the Raw Sequence Listing Error Report attached to this Office Action. In addition, Applicants have not submitted a statement that the paper and computer readable copies are identical and contain no new matter (37 C.F.R. 1.821(f)). Because these issues do not affect the ability to examine and search the claimed invention, the application has been examined. However, it is noted that for the response to this office action to be fully responsive, correction of the informalities is required.

Drawings

3. The drawings have been objected to for defects noted on the Form PTO-948. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 42-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, pp. 71427-71440 (available at www.uspto.gov) and the Examiner training Materials on Written Description also available at www.uspto.gov.

7. Claims 42-57 are genus claims. Claim 42 is directed to a genus of adenine nucleotide translocator (ANT) proteins from any source. Claim 44-51 are directed to the genus of human ANT proteins or any variants or fragments thereof, and Claims 52-57 are drawn to the genus of animal ANT proteins or any variants or fragments thereof. The specification defines a variant as a polynucleotide which encodes an analog having an insertion, deletion, or substitution (p. 18, lines 17-23) and a "fragment" as any ANT polypeptide that retains "essentially the same biological function or activity" as an ANT polypeptide (p. 20, beginning at line 1). The specification and claim do not place any limit on the number of amino acid substitutions, deletions, and/or additions

that may be made. Therefore, the scope of the claim includes variants and fragments of any length and sequence. The genus is highly variant because a significant number of structural differences between genus members is permitted and the specification and claims do not indicate what distinguishing attributes are shared by the members of such a genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is extremely variant, then the three species, ANT 1, ANT2, and ANT3 having the sequences defined by SEQ ID NO: 31-33 alone are insufficient to describe the genus of any ANT protein having any sequence and having any length. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 42-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Marzo et al. (Science (Sept. 25, 1998) 281(5385): 2027-2031).

10. Marzo et al. disclose a purified human ANT2 protein (p. 2029, Col. 1, lines 9-32, Fig. 2C, Fig. 4). ANT2 is considered a variant of ANT1 and ANT3. Therefore, Marzo et al. meets the limitations of Claims 42-46.

11. Claims 42-46 are rejected under 35 U.S.C. 102a as being anticipated by Fiore et al. (Biochimie (Feb. 1998) 80: 137-150).

12. Fiore et al. provides a review of mitochondrial ADP/ATP carrier proteins (also known as ANT proteins) and provides evidence that ANT proteins are very well known in the art. Figure 1 of the Fiore et al. reference provides an amino acid sequence alignment of 29 sequences of known ANT proteins from human, bovine, mouse, rat, as well as other sources. In particular, the sequences of human ANT 1, 2, and 3 are provided. The Fiore et al. reference indicates that the ANT proteins from human and animal sources have not only been isolated but are also fairly well characterized. For example, Fiore et al. state "the definite characterization of the ADP/ATP carrier as a transport protein was established after reincorporation of the isolated carrier into liposomes and reconstitution of transport" (p. 138, Col. 1, last 4 lines of the column) and the beef heart ADP/ATP carrier isolated in the presence of detergent is able to undergo the transition between two conformational states (p. 145, Col. 1, lines 1-9).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 43-57 rejected under 35 U.S.C. 103(a) as being unpatentable over Fiore et al. as applied to claims 42-46 above, and further in view of Rosenberg (Protein Analysis and Purification: Benchtop Techniques, (1996) Birkhauser, Boston, pages 335-347).

16. The teachings of Fiore et al. have been described above. Fiore et al. also disclose that a yeast strain containing an ANT carrying a polyhistidine tag at the C terminus was constructed to allow purification by immobilized metal ion affinity chromatography (p. 144, Col. 1, last paragraph). However, Fiore et al. do not teach a human or animal ANT fusion protein.

17. Rosenberg shows that it is standard in the art to construct fusions between a protein of interest and an enzyme (i.e. β-galactosidase (β-gal) (p. 336, lines 3-6 and section titled "Expression and Purification of lacZ and trpE Fusion Proteins") or an affinity tag (i.e. His-Tag or FLAG or GST (see p. 341-347)). Rosenberg teaches that using β-gal as the fusion partner provides an advantage because antibodies to β-gal can be used to affinity purify the fusion protein and to follow purification of the fusion protein by Western blot analysis of the various fractions. Rosenberg also teaches that a protease cleavage site can easily be engineered into the fusion so that the fusion partner can be separated from the protein of interest after purification (see p. 344, Section 11.15).

18. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention, to express the well known human and animal ANT protein sequences taught in Fiore et al. as fusion proteins wherein the fusion partner was a polypeptide or enzyme having affinity for a ligand. One would have been motivated to do so because such a protein would allow easier purification on an affinity column. Using β-gal as the fusion partner has the added benefit that the fusion protein can be easily monitored during purification (for optimization of purification conditions) or during expression (to localize the fusion protein in cells using the enzymatic activity of the β-gal protein).

19. Claims 43-50 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian et al. (Mol. Cell. Biol. (1986) 6(2): 626-634) in view of Fiore et al. as applied to Claims 42-46 above.

20. Adrian et al. disclose the expression of fusion proteins comprising *Saccharomyces cerevisiae* ADP/ATP translocator (ANT) proteins of various lengths (see p. 631, Fig. 5) and the enzyme β-galactosidase in an investigation of what amino acids are important in targeting the protein to the mitochondrial membrane. The study reveals that several of the fusion proteins were delivered to the mitochondria (see p. 630, Col. 2, lines 23-30; and p. 631, Table 1).

21. Adrian et al. do not teach that the ANT proteins were derived from human or animal sources.

22. As described above, Fiore et al. disclose the amino acid sequence alignment of 29 sequences of known ANT proteins from human and animal sources, and indicate that these proteins have been isolated (p. 145, Col. 1, lines 1-9).

23. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to express the human and animal ANT proteins described in Fiore et al. as fusion proteins as taught in Adrian et al. One having ordinary skill in the art would have been motivated to substitute human or animal ANT instead of the disclosed yeast ANT in order to study the mitochondrial localization sequences in human and animal ANT. Characterization of animal and more importantly human ANT proteins is essential to the development of diagnostic and treatment tools because as taught in Fiore et al. (p. 146, Col. 2), these proteins have a central role in

cellular energy metabolism and it is likely that dysfunction of these proteins is involved in mitochondrial disorders.

Additional References

24. Brandolin et al. (Biochemistry (1985) 24: 1991-1997), referenced in Fiore et al. above (reference number 48 , cited on page 145, Col. 1, first paragraph), provides another example that adenine nucleotide translocators from animals were very well known in the art at the time of the invention and that these proteins could be isolated and purified successfully. The Brandolin et al. reference describes the isolation and purification of an adenine nucleotide carrier protein (also known as adenine nucleotide translocator, see Fiore et al.) from beef heart mitochondria.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday-Friday from 7:30 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 306-4119. The fax phone number for Official Papers to this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Holly Schnizer, Ph.D.
April 19, 2000

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH D
PRIMARY EXAMINER